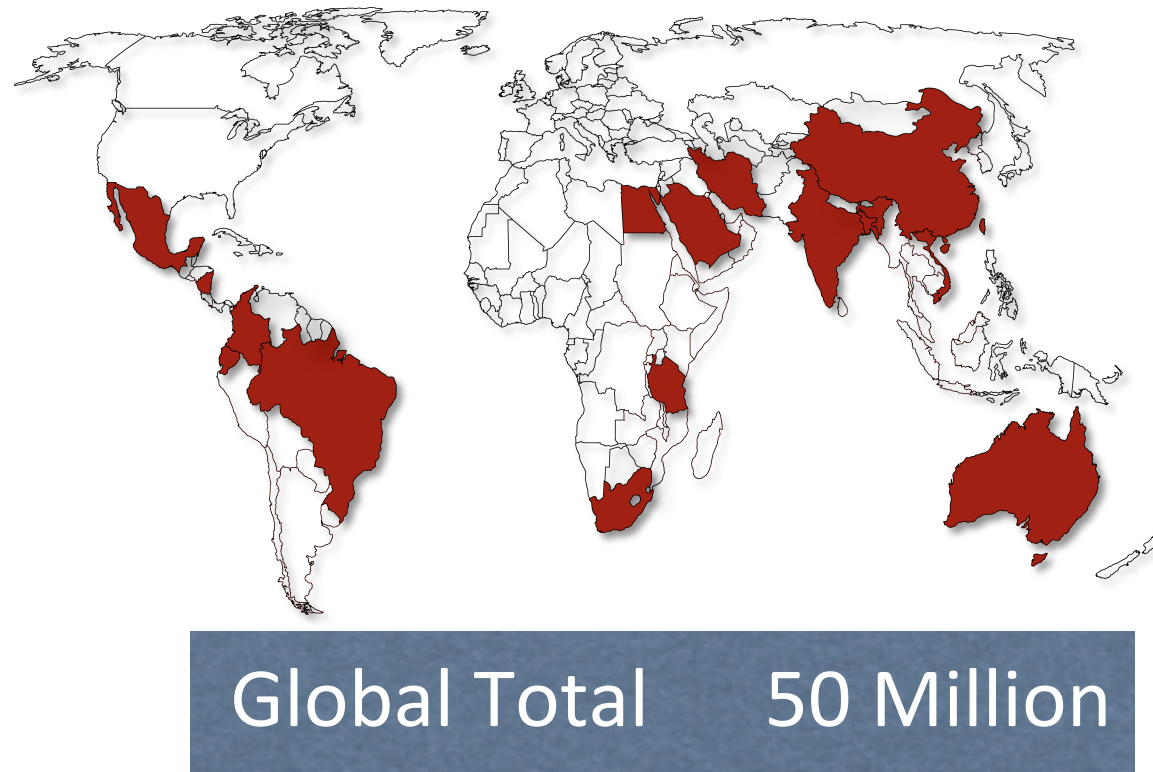


Discovery of New Drug Leads for Rare Parasitic Diseases

Anjan Debnath, Ph.D.

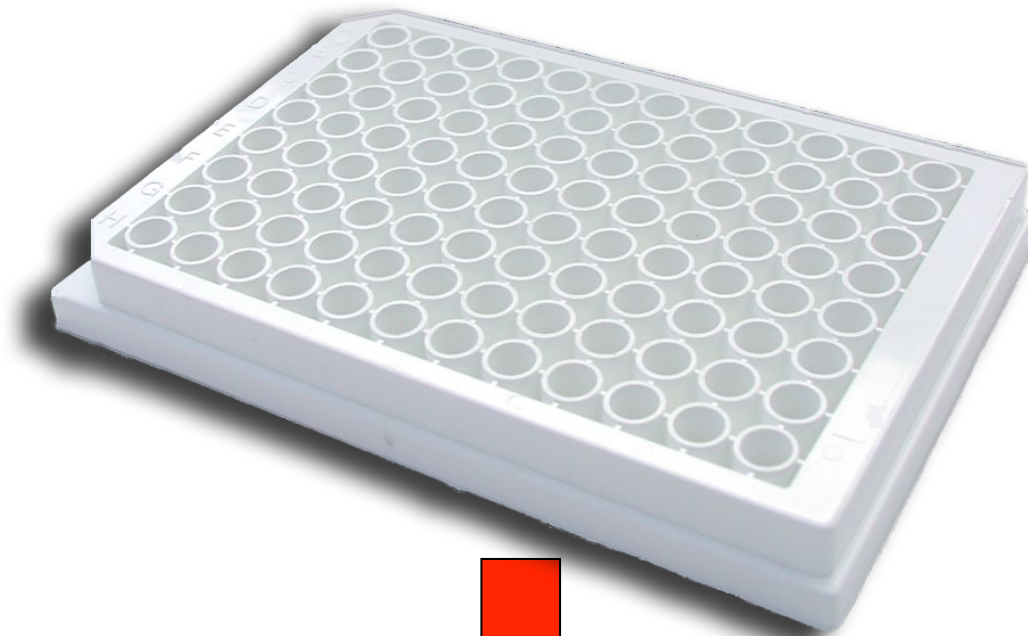


Amebiasis – a global but “neglected disease” caused by *Entamoeba histolytica*

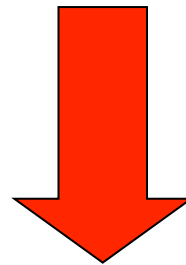


- 70,000 deaths each year
- 480 million at risk
- Current therapy with metronidazole and paromomycin
- A disease primarily of the poor

Development of a novel drug screen for *E. histolytica*

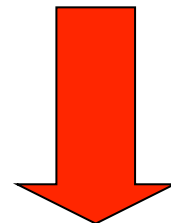


+ 5×10^3 parasites/well



48 hours @ 37°C in
Anaerobe Gas Pouch

Cell Titer Glo reagent (Promega) per well



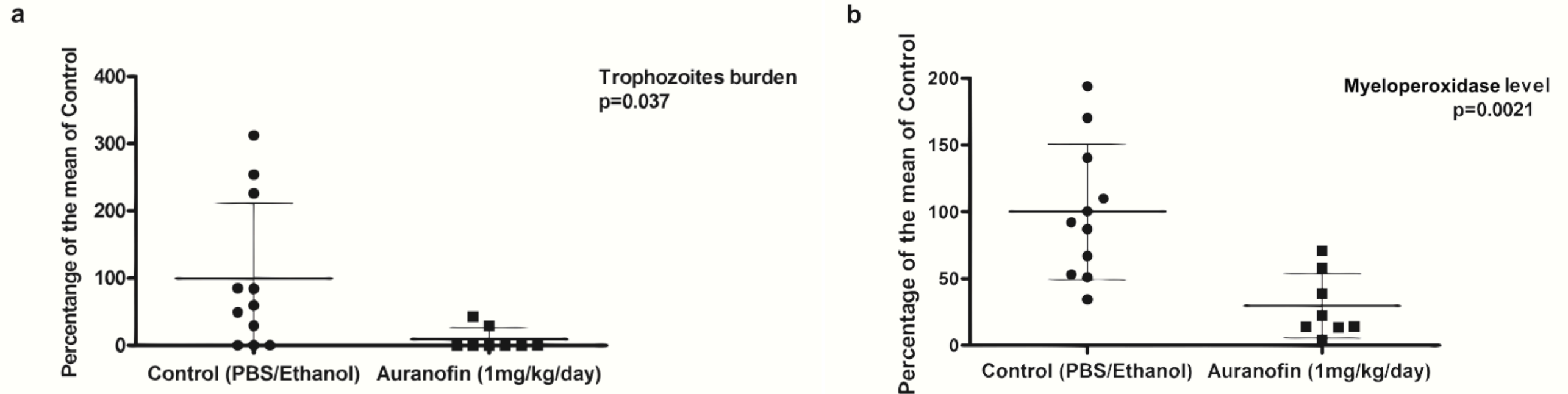
Record luminescence

Auranofin as a new drug lead for *E. histolytica*

Screened 910 drugs and bioactives

Compounds	EC ₅₀
Auranofin (Ridaura®)	0.5 µM
Metronidazole	5 µM

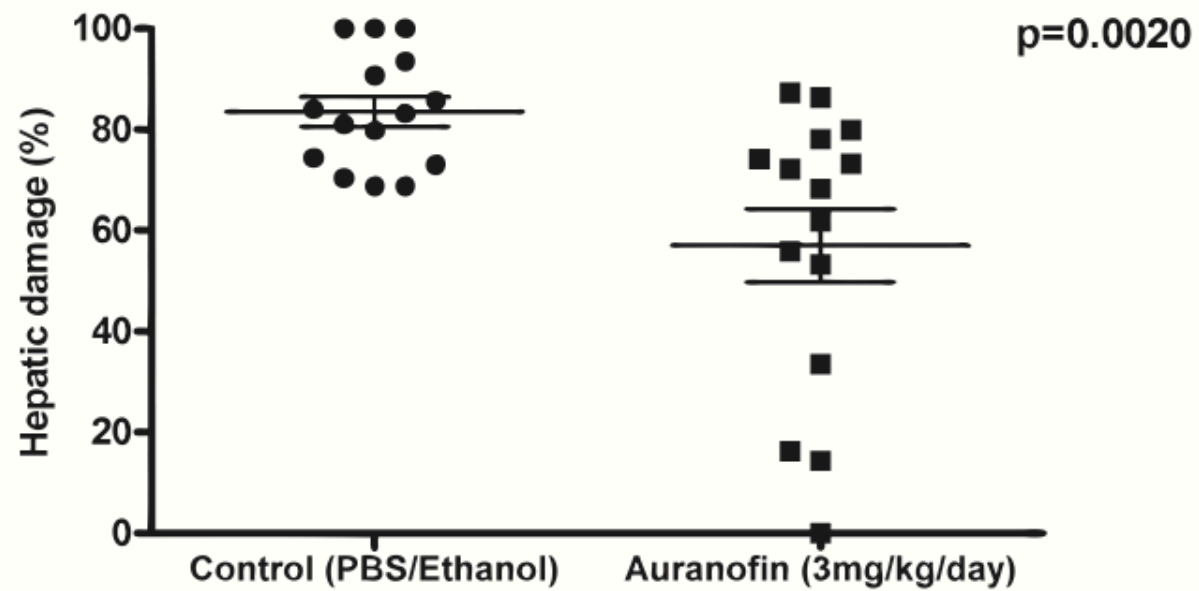
In vivo efficacy of auranofin for *E. histolytica*



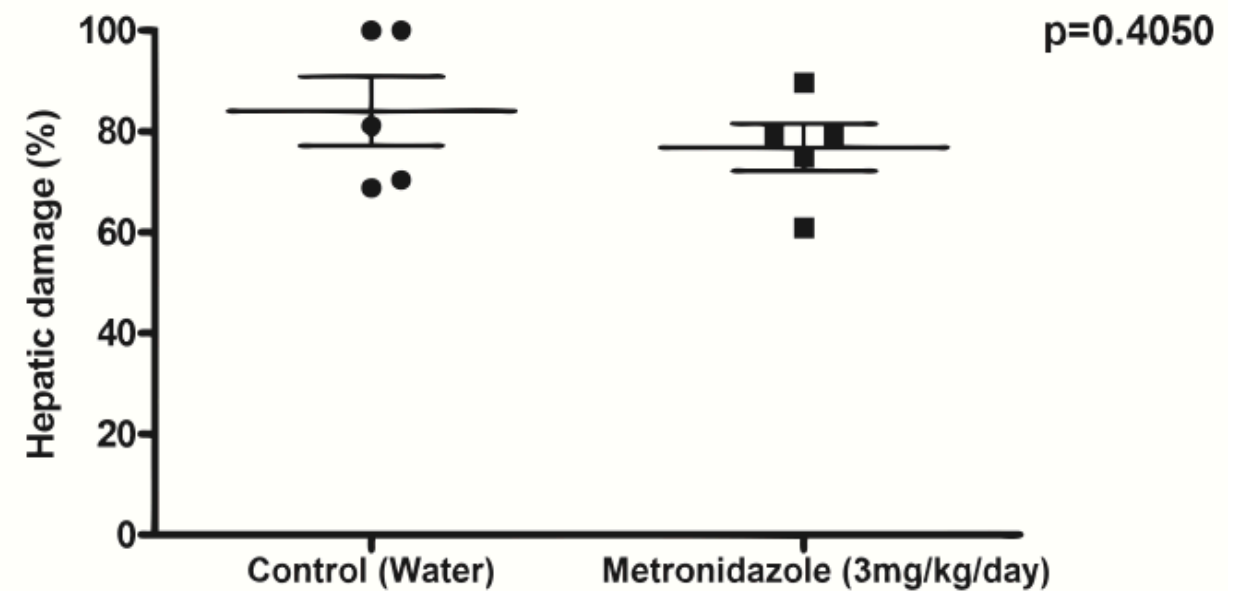
**Efficacy of auranofin in a mouse model of amebic colitis
after a single oral dose of 1 mg/kg/day for 7 Days**

Debnath *et al.*, Nature Medicine (2012)
Debnath *et al.*, Gut Microbes (2013)

Auranofin

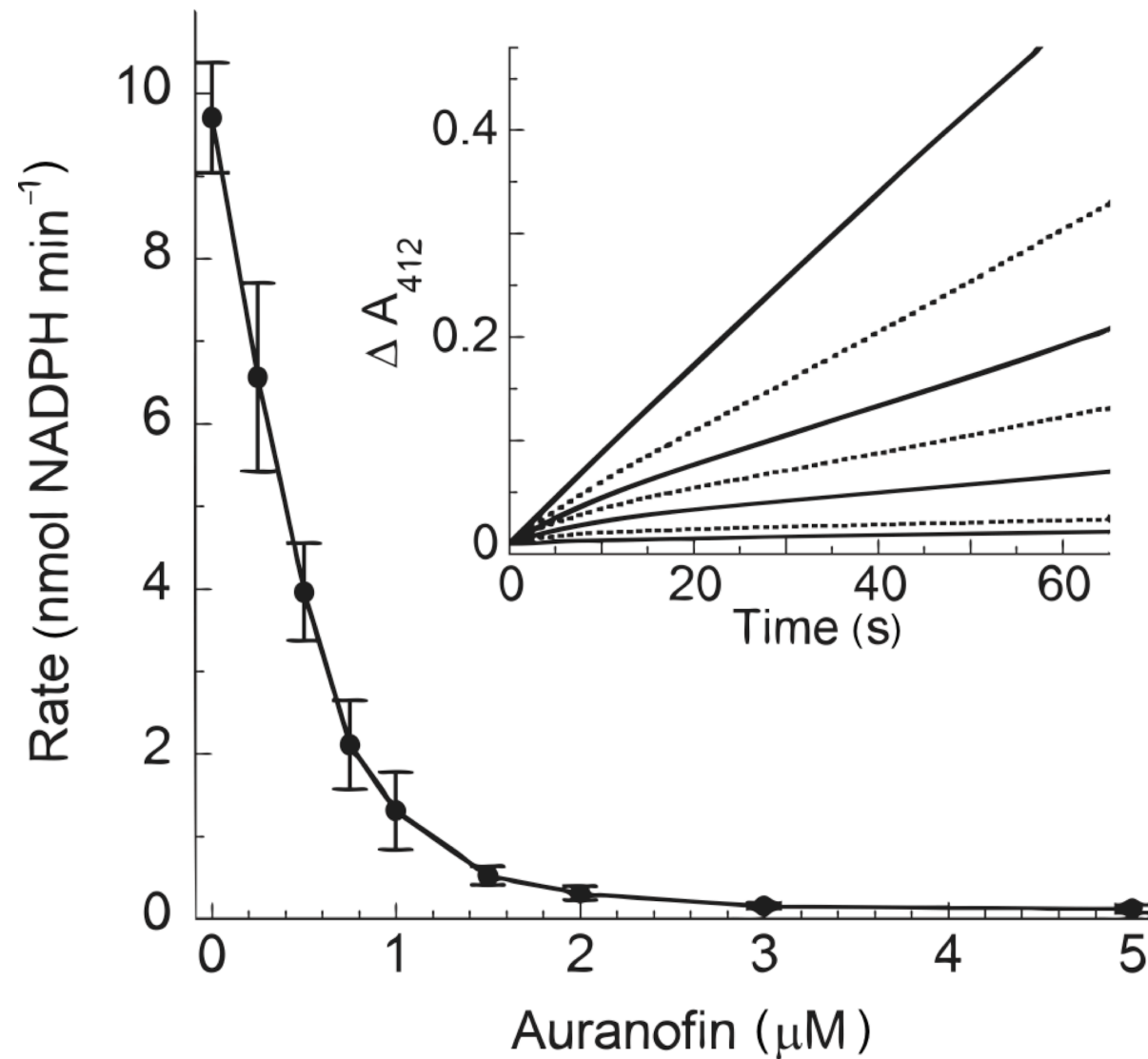


Metronidazole

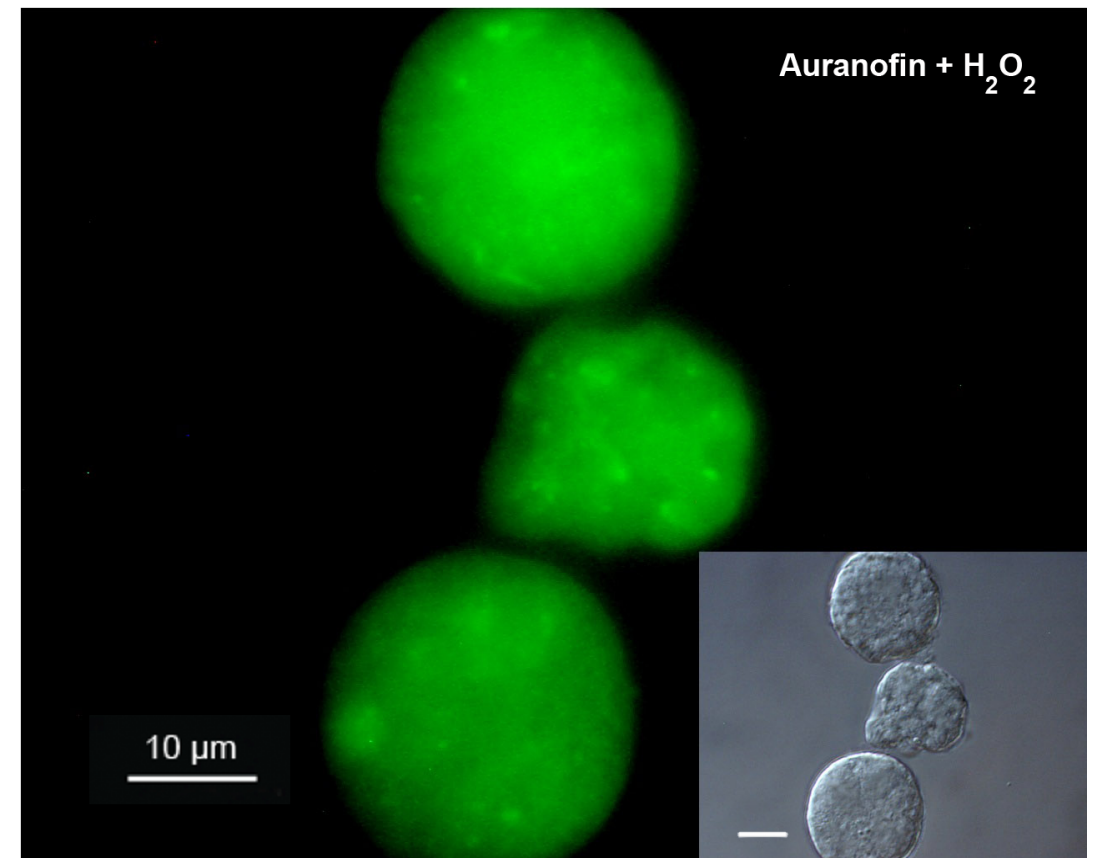
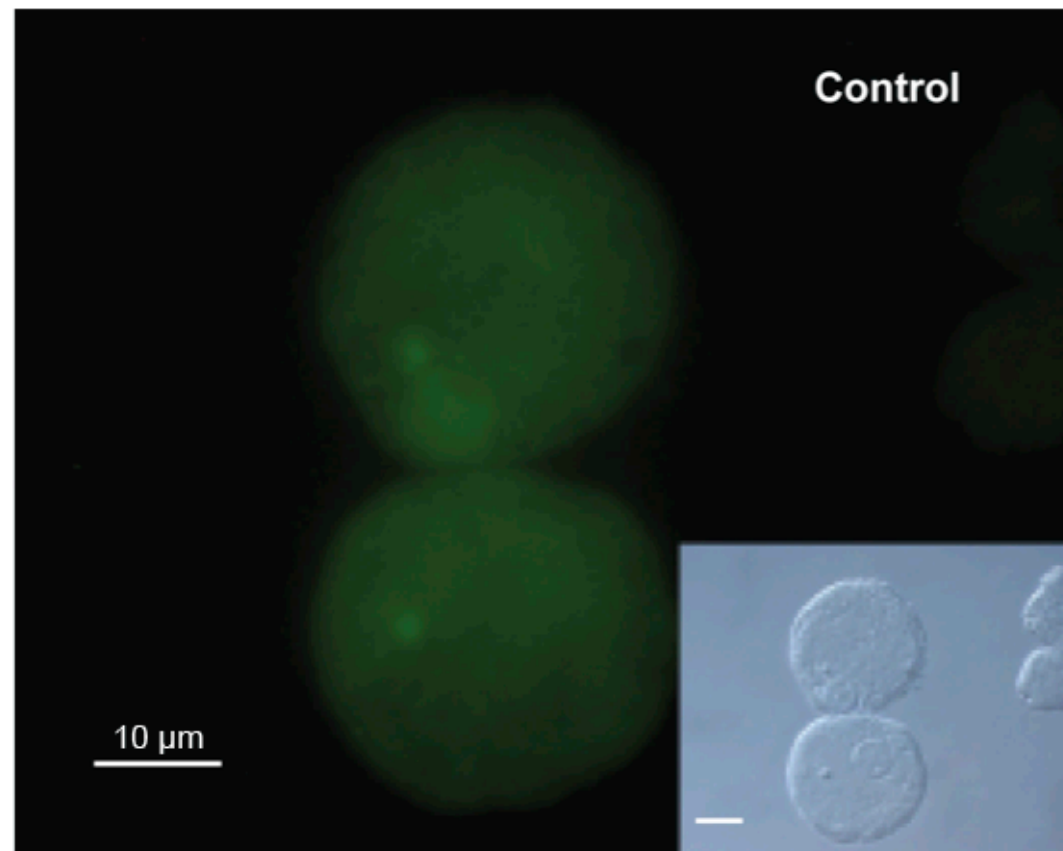


**Efficacy of auranofin in a hamster model of liver abscess
after a single oral dose of 3 mg/kg/day for 7 Days**

Auranofin's mechanism of action in *E. histolytica*



Auranofin targets parasite thioredoxin reductase



Auranofin causes reactive oxygen-mediated parasite killing

Auranofin received FDA Orphan Drug status for the treatment of amebiasis

By identifying a “repurposed drug” the cost and development time can be significantly reduced

Next steps

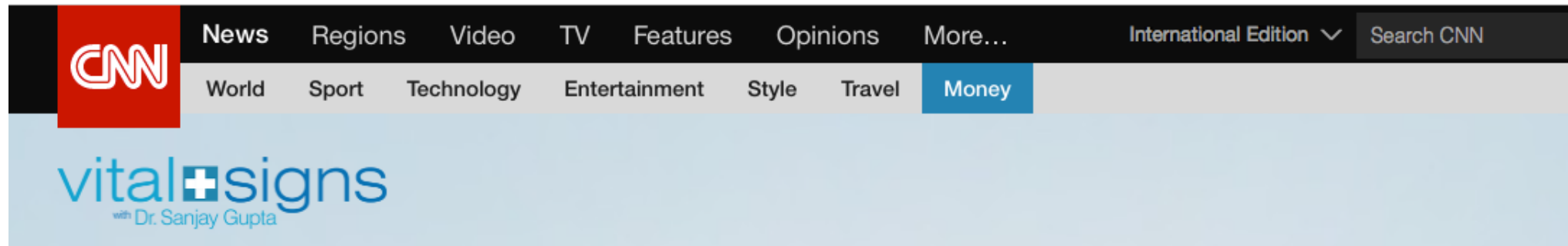
Giardiasis	280 Million
Cryptosporidiosis	500 Million
Trichomoniasis	174 Million
Lymphatic filariasis	128 Million
Onchocerciasis	37 Million

GLOBAL TOTAL

1.1 BILLION

- Clinical trial for amebiasis in Bangladesh by Dr. Sharon Reed of UCSD
- Clinical trial planning for other infections

Primary Amebic Meningoencephalitis (PAM) – a rare disease caused by *Naegleria fowleri*



Brain-eating amoeba kills 14-year-old star athlete



By Holly Yan, CNN

Updated 2232 GMT (0532 HKT) August 31, 2015 | Video Source: [KTRK](#)



Distribution of reported PAM cases

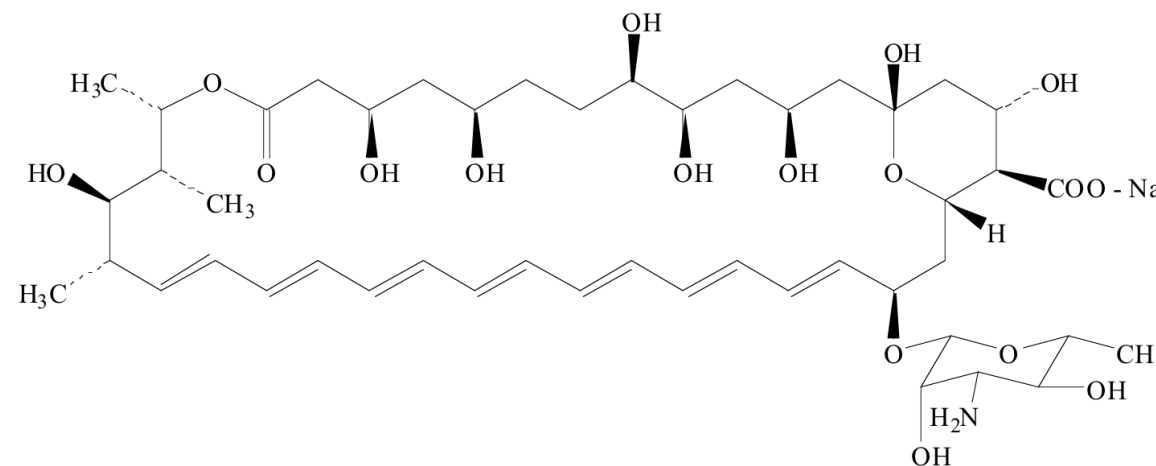


- 133 case reports of PAM have occurred in the US from 1962-2014
- Only 3 survivors in the US
- Mortality rate is greater than 95%
- Amphotericin B remains a cornerstone of therapy

Corifungin is active against *Naegleria*

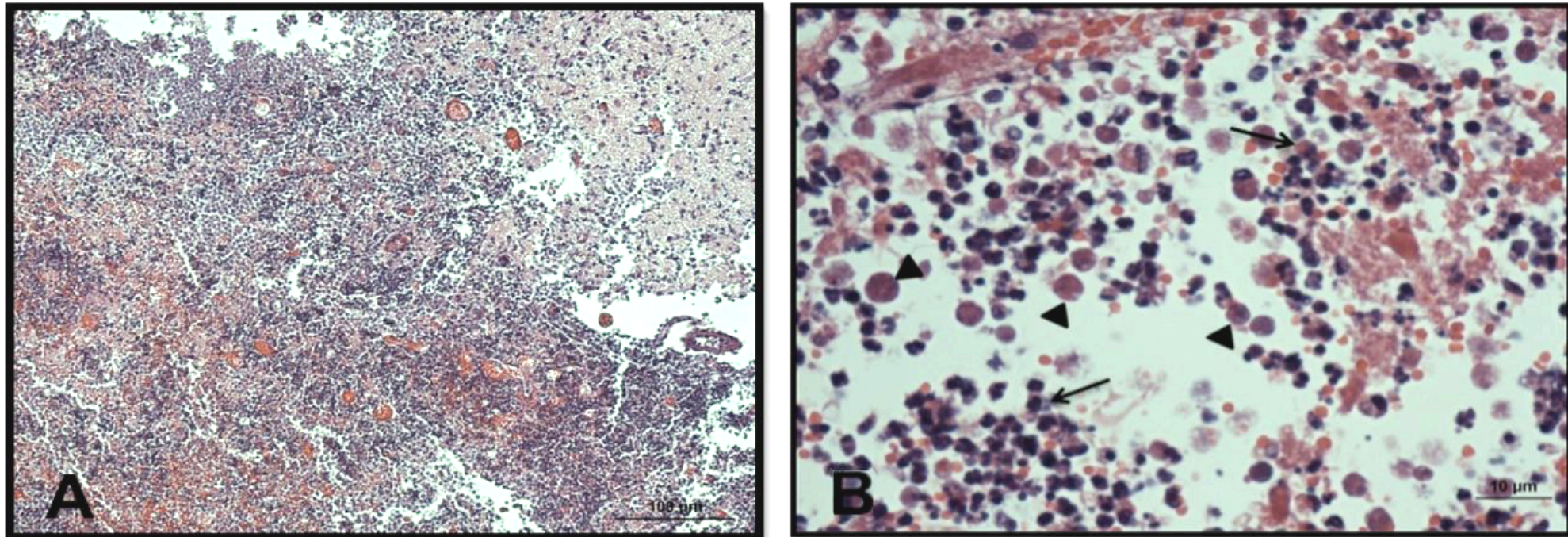
- Corifungin from Acea Biotech (San Francisco) is a broad-spectrum antifungal
- Amphotericin B EC₅₀ for *Naegleria* is 0.27 μM
- Corifungin EC₅₀ for *Naegleria* is 0.21 μM

	Molecular weight	Molecular formula	Water solubility
Corifungin	947.4	C ₄₇ H ₇₃ NO ₁₇ Na	very soluble: > 100 mg/ml
Amphotericin B	924.5	C ₄₇ H ₇₃ NO ₁₇	insoluble

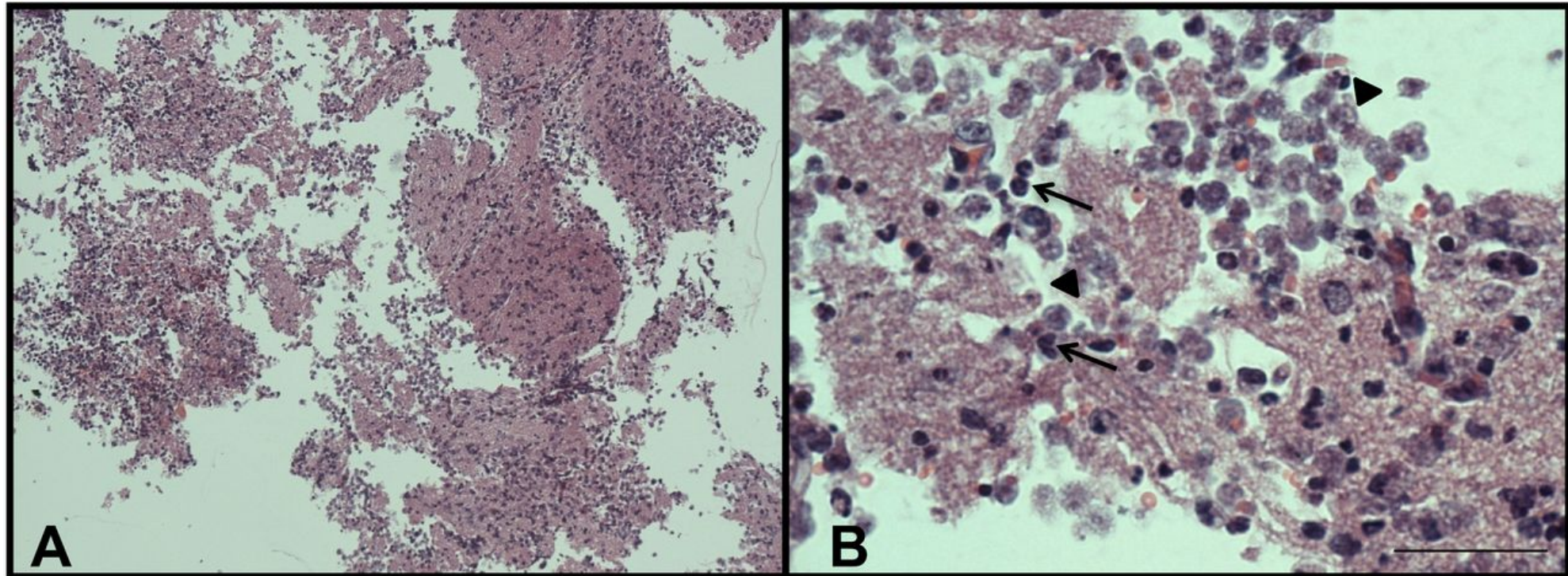


Chemical Structure of Corifungin

Light microscopy of olfactory bulbs in mice infected with *N. fowleri*

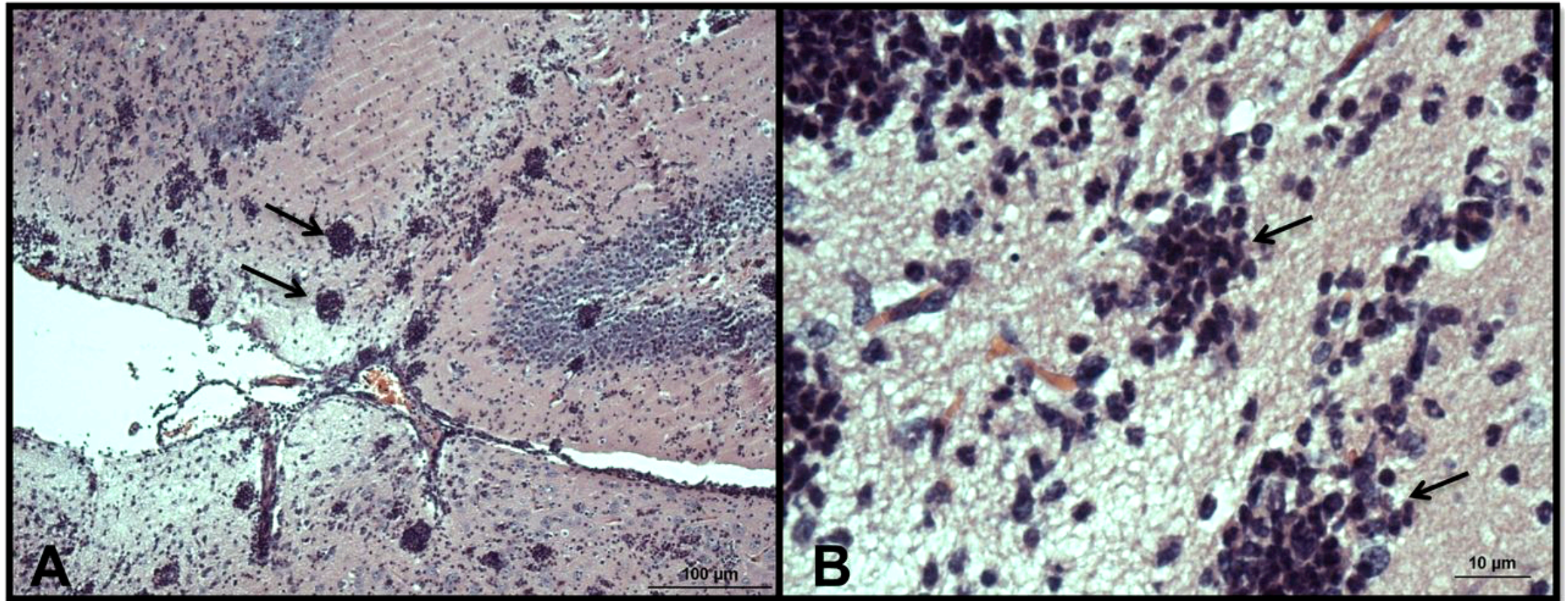


PBS treatment



9 mg/kg/day amphotericin B i.p. treatment for 10 days

In vivo efficacy of corifungin



Efficacy of corifungin in mouse model after intraperitoneal treatment with 9 mg/kg/day 10 days

Debnath *et al.*, Antimicrobial Agents & Chemotherapy (2012)

Survival and mean time to death of mice

Treatment group (treatment dose [mg/kg/day]) ^a	No. of mice	No. of surviving mice (%) ^b	Mean time to death (days) ^c
Control	10	7 (70)	12
Amphotericin B (9)	10	6 (60)	11
Corifungin (9)	10	10 (100)	None died

^a Control group received PBS.

^b Mice were held for 17 days after inoculation, and the cumulative percentage was recorded on daily basis.

^c The mean time to death was calculated based only on dead mice.

Orphan-drug designation of corifungin for PAM

Center for Discovery and Innovation in Parasitic Diseases (CDIPD) has received an orphan-drug status from the FDA for the following:

Name: Corifungin

Indication: Treatment of Amebic Meningoencephalitis

Next steps

- Phase I clinical trial of corifungin
- Using target-based approach to identify novel amebicidal compounds as new drug leads for *Naegleria*